

Cartilage repair in osteoarthritic patients: utopia or real opportunity?

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Abstract

As medical advances lengthen average life expectancy, osteoarthritis (OA) will become a larger public health problem – not only because it is a manifestation of aging but also because it usually takes many years to reach clinical relevance. OA is already one of the ten most disabling diseases in industrialized countries. The huge financial burden emphasizes the acute need for new and more effective treatments for articular cartilage defects, especially since there are few disease modifying drugs or treatments for OA. There is no cure for OA and the management of OA is largely palliative, focusing on the alleviation of symptoms. Recent longitudinal non-controlled trials suggest that autologous chondrocyte transplantation techniques, which are indicated for young people with traumatic cartilage defects, could also be used in degenerative defects of elderly people with OA. This report discusses this therapeutic opportunity in view of some recently published data.

Introduction and context

In adults, damaged cartilage has a very limited capacity for self-healing due to the absence of blood vessels, the low intrinsic density of chondrocytes, and the low turnover of the extracellular matrix [1]. The absence of stem cells and the low capacity of resident chondrocytes to migrate and proliferate also reduce cartilage regeneration capacity. Therefore, numerous methods have been proposed to repair cartilage defects in young or osteoarthritis (OA) subjects [2]. Intrinsic repair can be stimulated by bleeding induced by drilling or microfracturing the subchondral bone. Fibrin clot formation, vascular invasion, and recruitment of stem cells into the defect result in the formation of scar tissue that is inferior biomechanically to normal cartilage and susceptible, therefore, to degeneration.

In osteochondral transplantation (or mosaicplasty), osteochondral plugs are transferred from undamaged and relatively non-weight-bearing regions to a debrided site. However, studies have shown that this technique results in donor site morbidity and extensive chondrocyte death in the margins of the osteochondral plugs.

One option to treat focal cartilage lesions is autologous chondrocyte implantation (ACI), a procedure developed in the late 1980s to treat traumatic and symptomatic cartilage lesions in the knees of young adults. The idea behind the ACI procedure is to take a cartilage biopsy from the knee by arthroscopy, to isolate cells and grow them in the lab and, once millions of cells have been grown, to implant them into the area of cartilage damage beneath a periosteal flap or a collagen sheet sutured to the surrounding healthy cartilage rim.

More recently, matrix-assisted autologous chondrocyte implantation (MACI) has been proposed as an alternative to ACI. This technique uses a biomaterial as a chondrocyte carrier that is directly implanted in the lesion [3-5]. The matrix can be synthetic, including but not limited to poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid) copolymer, poly(ethylene oxide), or poly(propylene oxide) polymers that all gel at body temperature, ceramic composite and hydrogel-containing polyethylene glycol polymer-based derivatives [6], or natural substances such as fibrin, collagens, alginate, agarose, chitosan, and hyaluronic acid. These

substances have been used to design and produce scaffolds in a rich variety of configurations, including woven and non-woven meshes [7], sponges, foam, glues [8], bilayer or trilayer composites [9] and, more recently, small-size magnetic beads [10,11]. To promote chondrogenesis (differentiation to chondrocyte-like cells) and scaffold integration, many MACI systems using growth factors, either attached to the scaffolds or through recombinant expression, have been proposed [12]. Several studies have also shown that pulsed electromagnetic field and continuous passive motion may promote chondrogenesis and implant integration to the existing cartilage [13]. Until now, ACI/MACI techniques have been reserved for patients who meet the following criteria [14]: age 15-60 years; body mass index (BMI) ≤ 35 ; presence of disabling pain and/or knee locking; focal articular cartilage defect down to but not through the subchondral bone on a load bearing surface of the femoral condyle (medial, lateral, trochlear) (not in the patella); size of defect < 7 mm in depth, < 6 cm in length, and $1.6-10$ cm² in area; stable knee with intact meniscus and normal joint space on X-ray; no active inflammatory or other arthritis, clinically and by X-ray; procedure is not being done for treatment of degenerative arthritis (OA); failure of conservative therapy (minimum of 2 months of physical therapy) as well as established surgical interventions (i.e., microfracture, drilling, abrasion) – diagnostic arthroscopy, lavage, or debridement are not considered adequate to meet this criterion; cooperation with post-operative weight-bearing restrictions and activity restrictions together with a potential for completion of post-operative rehabilitation; and informed consent with realistic expectations.

Recent advances

Currently, ACI is contraindicated in OA because the risks of complications and failure are high and clinical superiority has not been demonstrated compared with other treatments. In young adults with traumatic chondral lesions, re-operation is a common sequel of ACI with an incidence of 15-30% [15,16]. Periosteal hypertrophy and delamination, which account for 22.1% and 17.7%, respectively, of adverse effects reported to the US Food and Drug Administration, frequently require ACI site debridement [17]. Failure of ACI occurs in 4-22% of patients depending on defect traits and duration of follow-up [18]. The rate of failure increases with time from surgery and age. A study of single condylar defects reported 5% failure at 2 years, which increased to 22.5% at 5 years. One comparison of ACI by patient age demonstrated good to excellent results in 85.7% of patients younger than 20 years compared with 55.9% in those older than 40 years [19].

Recently, an extensive case report has shown that MACI based on a bioresorbable two-component gel-polymer scaffold is effective for the treatment of focal degenerative cartilage defects of the knee in subjects between 25 and 50 years of age [20]. This product is composed of fibrin and a polymer-based scaffold of polyglycolic/polylactic acid (polyglactin, vicryl) and polydioxanone. In this study, 18 patients with preoperatively radiologically confirmed OA and a Kellgren-Lawrence score of 2 or more were included and followed up for 4 years. The average age of patients (8 females and 10 males) was 35 years (25-50 years), the mean BMI was 25 (ranging from 19 to 24) and mean defect size was 4 cm² (2-6 cm²). Two patients had to undergo surgery and received a total knee prosthesis. Clinical improvement has been assessed by different scoring systems, including the Lysholm and International Cartilage Repair Society (ICRS) scores and the Knee injury and Osteoarthritis Outcome Score (KOOS). After 1 year, mean scores improved between 30% and 50% compared with the pre-operative situation, depending on which score was analyzed. The clinical results 1 year after implantation of the scaffold were good and remained stable for at least 4 years. This indicates a significant decrease in pain and disability as well as a significant increase in quality of life. However, nine patients were subjected to second-look arthroscopy due to symptoms such as persistent grinding, catching pain, or swelling. Magnetic resonance imaging performed 4 years after transplantation in 17 patients showed a complete filling of the defect with cartilage repair tissue in 11 patients. In five patients, the defects were filled more than 50% and one patient showed a defect fill of less than 50%. The cartilage signal in 16 out of 17 defects was normal or showed a slight alteration of the signal. Strong to moderate subchondral edema was evident in 6 patients, and 11 out of 17 patients showed no or mild edema. Five patients showed moderate to strong signs of knee joint effusion. No to mild knee joint effusion was evident in 12 out of 17 patients treated at 4-year follow-up. These results are promising but need to be reproduced in older patients with chondrocytes affected by the aging processes.

In a retrospective study by Minas *et al.* [21], 56 patients ≥ 45 years of age were treated with ACI using periosteal flap. The mean transplant size was 4.7 cm² per defect (range, 1-15 cm²) and 9.8 cm² per knee (range, 2.5-31.6 cm²). There were eight failures (14%), mainly in patients receiving workers' compensation, and 24 additional arthroscopic surgical procedures for periosteal-related problems and adhesion. At their latest available follow-up, 72% of patients rated themselves as good or excellent, and 78% felt improved and would again choose ACI as a treatment option.

Implications for clinical practice

These studies, even if they are limited to prospective or retrospective non-controlled trials, suggest that ACI/MACI systems could be used to prevent or delay total joint replacement in OA. Is this goal utopian or a real opportunity? These repair techniques are invasive, associated with some complications (locking of the joint and adhesions, extension deficit, recurrent knee effusion, and so on) and have an approximately 10% risk of failure. ACI/MACI show great promise as treatments for chondral lesions, with a potential for them to be highly cost effective. But at present this has not been demonstrated and recommendation of this technique for the treatment of cartilage defects in OA joint can not yet be justified. The superiority of ACI/MACI compared with other OA treatments, such as hyaluronic acid injection or other surgical procedures (debridement, microfractures), needs to be demonstrated. Further, these methods require a complex process of tissue harvest, cell culture, scaffold implantation and finally post-operative rehabilitation.

What are the clinical benefits that justify this investment in OA? Promising developments are underway with regards to cell-based techniques in combination with scaffolds, growth factors, and gene therapy. Unfortunately, this effort has not been followed by appropriate or sufficient clinical studies to assess these new methods and to compare them with existing systems. Further research is needed to simplify the implantation procedure and to improve the success level. OA patients are generally older and heavier than the population included in the current studies and we lack data on the incidence of failure in this population. Altogether, the use of ACI or MACI techniques in OA patients remains experimental but constitutes a real opportunity for such patients in the next decade. The main problems still to be resolved are how to produce a hyaline cartilage rather than a fibrocartilage, how to facilitate the integration of the repair within the surrounding tissue, and how to simplify the implementation procedure.

Abbreviations

ACI, autologous cell implantation; ICRS, International Cartilage Repair Society; KOOS, Knee injury and Osteoarthritis Outcome Score; MACI, matrix assisted cell implantation; OA, osteoarthritis.

Competing interest

The authors declare that they have no competing interests.

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